The association between Sarcopenia and Fracture in the WHI

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Background: Osteoporosis

Low bone density is a state of compromised bone strength

Osteoporotic fractures result in increased morbidity, mortality, and healthcare costs Braithwaite

Fracture events occur disproportionately in older adults, due in part to the decline in bone mineral density (BMD) Beavers

The prevalence of low bone density in women in US is 37-50-67% at the femoral neck Looker

- Low bone density increases in women until about age 70 and converts into osteoporosis
- Prevalence of low bone density rises to 87% in women 80+ Looker

Background: Sarcopenia

Sarcopenia is defined as the loss of muscle mass with increasing age

- No agreed upon definition
  - Newer definitions incorporate a strength & physical performance component

- Associated with a decline in strength, mobility disability, and physical function Janssen
- Prevalence of sarcopenia varies widely by definition, ranging from 9 – 40%

Definitions of Sarcopenia

	Low Lean Mass	Weakness	Slowness	Summary
Name	Definition	Definition	Definition	Definition
Baumgartner (1998)	ALM/ht^2	NA	NA	Low Lean Mass ≤ 7.23 kg/m^2

Definitions of Sarcopenia

	Low Lean Mass	Weakness	Slowness	Summary
Name	Definition	Definition	Definition	Definition
Newman et al (2003)	Residual of actual ALM-Predicted ALM	NA	NA	Low Lean Mass adjusted for fat & height

Definitions of Sarcopenia

	Low Lean Mass	Weakness	Slowness	Summary
Name	Definition	Definition	Definition	Definition
EWGSOP (2010)	ALM/ht^2 ≤ 7.23kg/m^2	Grip Strength < 30 kg	Gait Speed ≤0.8 m/s	Low Lean Mass + weakness OR slowness
International Working Group (2011)	ALM/ht^2 ≤ 7.23kg/m^2	NA	Gait Speed < 1.0 m/s	Low Lean Mass + slowness
FNIH Sarcopenia Project (2014)	ALM/BMI <.789	Grip Strength < 26kg	Gait Speed ≤ 0.8m/s	Low Lean Mass + weakness OR Low Lean Mass + weakness & slowness

Prevalence of Sarcopenia

Baumgartner et al

	Baumgartner, 1998 New Mexico Elder Health Survey		
Method	ALM/ht^2 (1)		
Age	70-74	75-80	>80
Men	19.8%	26.7%	52.6%
Women	23.1%	35.9%	43.2%

[1] ALM=Appendicular lean mass/ht^2 –gender specific 2 SD below young adult mean

Prevalence of Sarcopenia

Baumgartner et al, Dufour et al

	Baumgartner, 1998 New Mexico Elder Health Survey			Dufour, 2012 Framingham Heart Study	Dufour, 2012 Framingham Heart Study
Method	ALM/ht^2 (1)			ALM/ht^2 (1)	Residuals (2)
Age	70-74	75-80	>80	70s	70s
Men	19.8%	26.7%	52.6%	19.0%	25.0%
Women	23.1%	35.9%	43.2%	13.0%	24.0%

[1] ALM=Appendicular lean mass/ht^2 –gender specific 2 SD below young adult mean

[2] Residuals of regression (Newman et al) – gender specific

Prevalence of Sarcopenia Baumgartner, Dufour, Newman

	Baumgartner, 1998 New Mexico Elder Health Survey			Dufour, 2012 Framingham Heart Study	Dufour, 2012 Framingham Heart Study	Newman, 2003 Health ABC
Method	ALM/ht^2 (1)			ALM/ht^2 (1)	Residuals (2)	Residuals (3)
Age	70-74	75-80	>80	70s	70s	70-79
Men	19.8%	26.7%	52.6%	19.0%	25.0%	20.0%
Women	23.1%	35.9%	43.2%	13.0%	24.0%	20.0%

[1] ALM=Appendicular lean mass/ht^2 –gender specific 2 SD below young adult mean

[2] Residuals of regression – gender specific

Background: Sarco-osteopenia

"Sarco-osteopenia" may represent a greater risk of fracture than either osteoporosis or sarcopenia alone Binkley

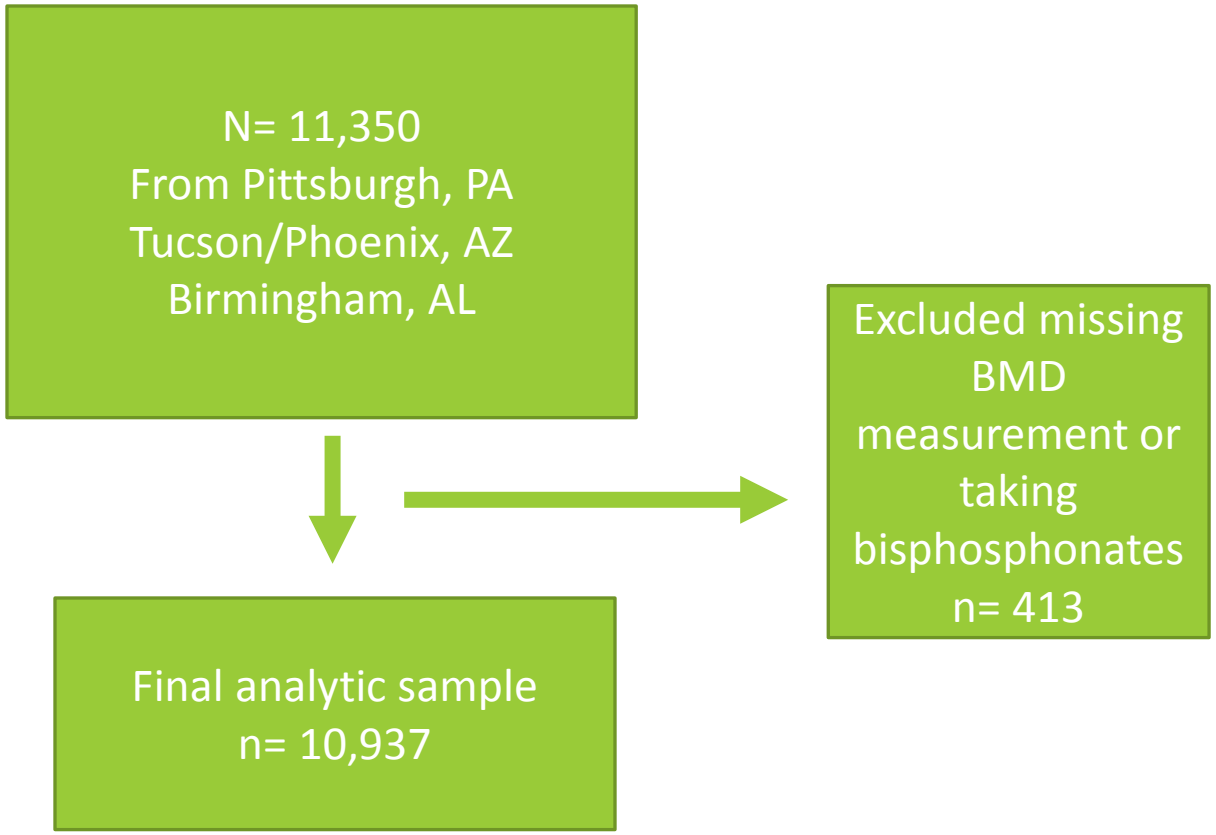
- In men, a nearly 4 fold risk of fracture was seen in men with this combination compared to men without and men with only low bone mass Chaloub

Methods- Study Population

Women's Health Initiative

- 161,808 women aged 50-79 years at baseline
  - Free of serious medical conditions and post-menopausal
  - 40 US clinical centers
  - Observational & RCT (diet, hormone therapy, and calcium +vitamin D supplementation)

Methods- Sample



Methods- Femoral Neck Bone Mineral Density

Standardized procedures for positioning and scan analysis

Femoral neck BMD selected because in FRAX it is the choice for risk assessment

Low Bone Density is defined as femoral neck T-score ≤ -1.0 based on the NHANES III reference database Bianchi

T score: your BMD results are compared to the "ideal" BMD (young white female)

- Normal BMD is within 1 SD
- Low Bone Density is between 1- 2.5 SD below
- Osteoporosis is greater than 2.5 SD below

Methods- Sarcopenia

Based on appendicular lean mass (ALM) derived from the sum of lean mass in the upper and lower extremities, removing bone mineral content from whole body DXA scan

Newman et al method [Newman]

- Corrected the ALM for fat mass and height
- Perform linear regression to model the association between ALM, fat mass, and height
- The 20th percentile of the distribution was used as the cut-point
- This method has been shown to be a stronger predictor of mobility and disability limitations in Health ABC and Framingham studies

Sarcopenia Definitions

Newman et al

Odds Ratio (OR) of Having an EPESE Score of Less than 10 by Sarcopenia Definition in Men and in Women in Health ABC

	aLM/ht2	Residuals
	OR (95% Confidence Interval)	
Men		
Crude	1.4 (1.0–1.8)	1.4 (1.1–1.9)
Age &race adjusted	1.6 (1.2–2.2)	1.9 (1.4–2.7)
Fully Adjusted	1.5 (1.1–2.1)	1.8 (1.3–2.5)

Adjusted for age, race, smoking, drinking, comorbidity, and physical activity.

For ratio of appendicular lean mass and height squared (aLM/ht2), also adjusted for body mass index (BMI) (continuous).

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Methods- Other Measurements

Information on potential confounders and covariates was obtained from self-report questionnaires, clinic interviews, and physical measures at baseline

Age, race, clinic site, history of fracture, fall history, smoking status, alcohol consumption, hormone use, corticosteroid use, treated diabetes, physical activity, physical function, co-morbid conditions, dietary habits (vitamin D & calcium)

Methods- Potential Confounders

Age

Race

Clinic site

History of fracture

Fall history in past 12 months

Smoking status

Alcohol consumption

Physical activity

Physical function

Co-morbid conditions

Dietary intake

Hormone use

Corticosteroid use

Treated Diabetes

Methods- Fractures

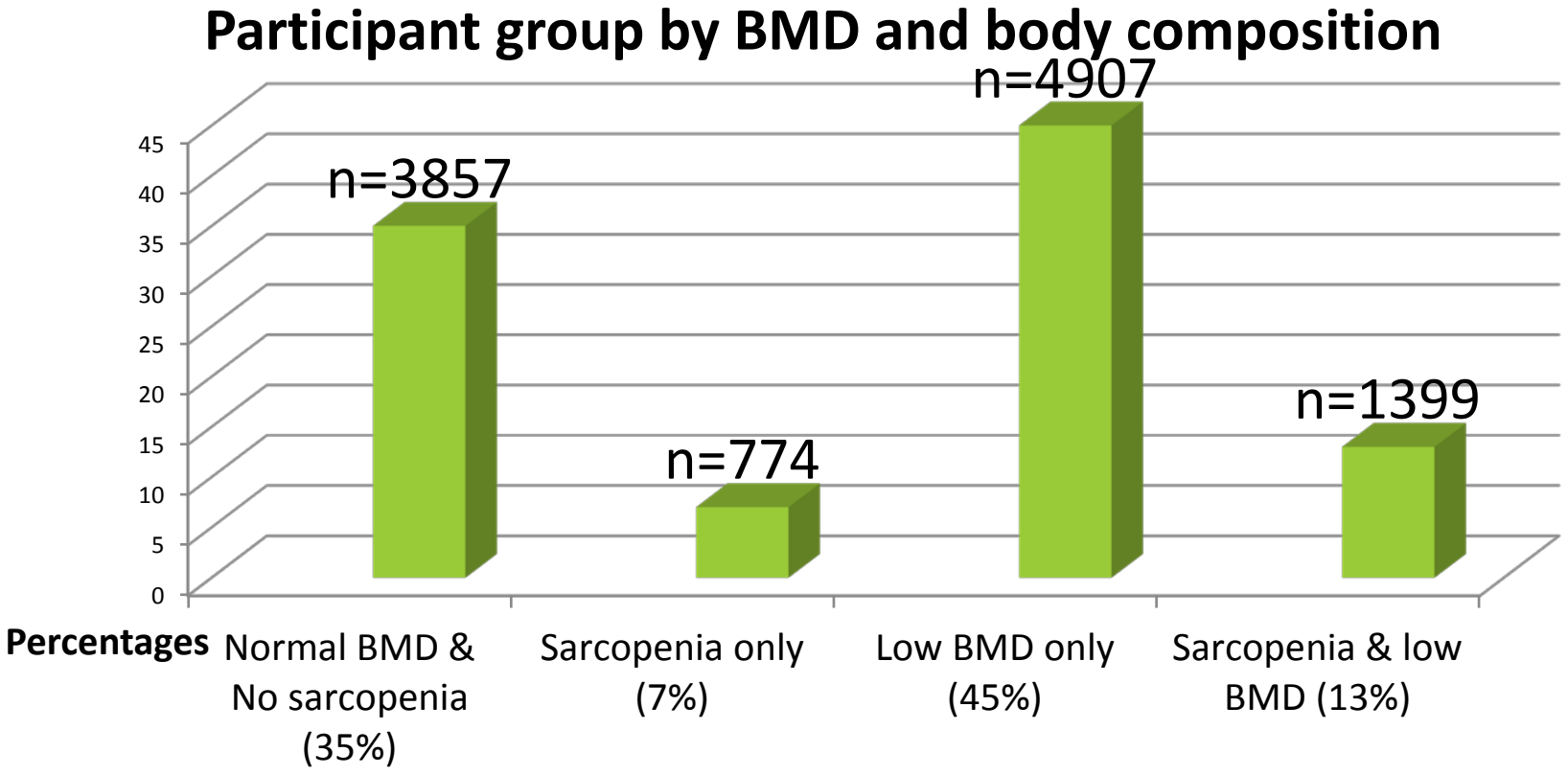
Incident fractures obtained prospectively

- Observational Study- annual
- Clinical trial- semi-annually

Excluded fractures of the fingers, toes, face, sternum, ribs, skull, and pathological fractures

Hip fractures were locally and centrally adjudicated, all other fractures were adjudicated during the active study

Statistical Approach



Baseline Characteristics	Normal BMD, No Sarcopenia n=3857	Sarcopenia n=774	Low BMD n=4907	Low BMD, Sarcopenia n=1399	p-value
Age	60.8 ± (7.0)	62.0 ± (7.2)	65.0 ± (7.1)	65.3 ± (7.0)	a,b,c,d,f
Race/White (%)	64.1	82.0	87.0	91.1	a,b,c,d,e,f
Education (%)					a
Less than high school	11.3	10.4	8.7	9.0	
High School/Vocational School	59.6	60.7	59.9	61.5	
College +	29.1	28.9	31.4	29.5	

[a] normal versus low BMD, [b] normal versus sarcopenia, [c] normal versus low BMD +sarcopenia, [d] low BMD versus sarcopenia, [e] low BMD versus low BMD+sarcopenia, [f] sarcopenia versus low BMD+sarcopenia

Baseline Characteristics	Normal BMD, No Sarcopenia n=3857	Sarcopenia n=774	Low BMD n=4907	Low BMD, Sarcopenia n=1399	p-value
Appendicular Skeletal Mass (total) Kg	16.6 ± (2.9)	13.0 ± (1.9)	14.4 ± (2.2)	12.0 ± (1.6)	a,b,c,d,e.f
BMI kg/m^2	31.0 (6.3)	29.2 (5.8)	26.5 (4.9)	26.2 (4.3)	a,b,c,d,e,f
Baseline BMD g/cm^2 (femoral neck)	.84 (.09)	.82 (.08)	.64 (.07)	.64 (.07)	a,b,c,d,f
Current Smoker (%)	8.3	6.5	8.3	7.5	b,c,d

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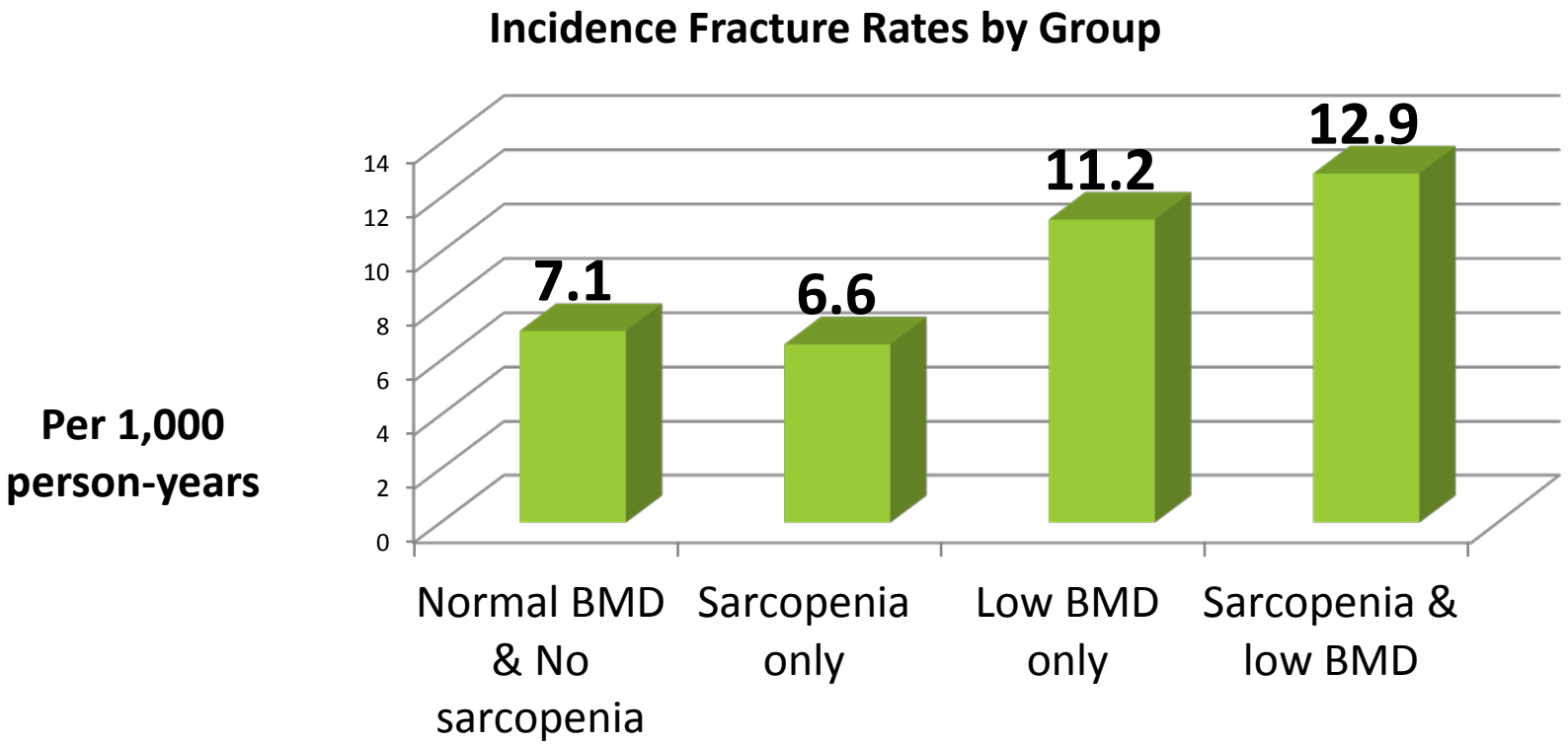
Baseline Characteristics	Normal BMD, No Sarcopenia n=3857	Sarcopenia n=774	Low BMD n=4907	Low BMD, Sarcopenia n=1399	p-Value
Alcohol Use (servings/week)	1.6 ± (4)	1.7 ± (4.1)	1.9 ± (4.3)	1.6 ± (3.8)	a,e
Fall history %					c,e,f
≤ 1 fall	70.7	72.3	71.3	67.5	
>1 fall	29.3	27.7	28.7	32.5	
History of fracture %	30.8	28.9	42.8	44.2	a,c,d,f
Use of hormones %	53.9	66.5	48.0	58.1	a,b,c,d,e,f

[a] normal versus low BMD, [b] normal versus sarcopenia, [c] normal versus low BMD +sarcopenia, [d] low BMD versus sarcopenia, [e] low BMD versus low BMD+sarcopenia, [f] sarcopenia versus low BMD+sarcopenia

Baseline Characteristics	Normal BMD, No Sarcopenia n=3857	Sarcopenia n=774	Low BMD n=4907	Low BMD, Sarcopenia n=1399	p-value
Physical Activity MET-hours/week	10.9 ± (14.1)	9.0 ± (11.4)	12.9 ± (14.5)	9.4 ± (11.9)	a,b,c,d,e
Treated Diabetes, n	18	43	10	23	
RAND-36 Score %					a,b,c,d,e,f
> 90	25.0	29.5	16.1	21.1	
≤ 90	75.0	70.5	83.9	78.9	

[a] normal versus low BMD, [b] normal versus sarcopenia, [c] normal versus low BMD +sarcopenia, [d] low BMD versus sarcopenia, [e] low BMD versus low BMD+sarcopenia, [f] sarcopenia versus low BMD+sarcopenia

Statistical Approach- Poisson Model



Statistical Approach- Fracture Type

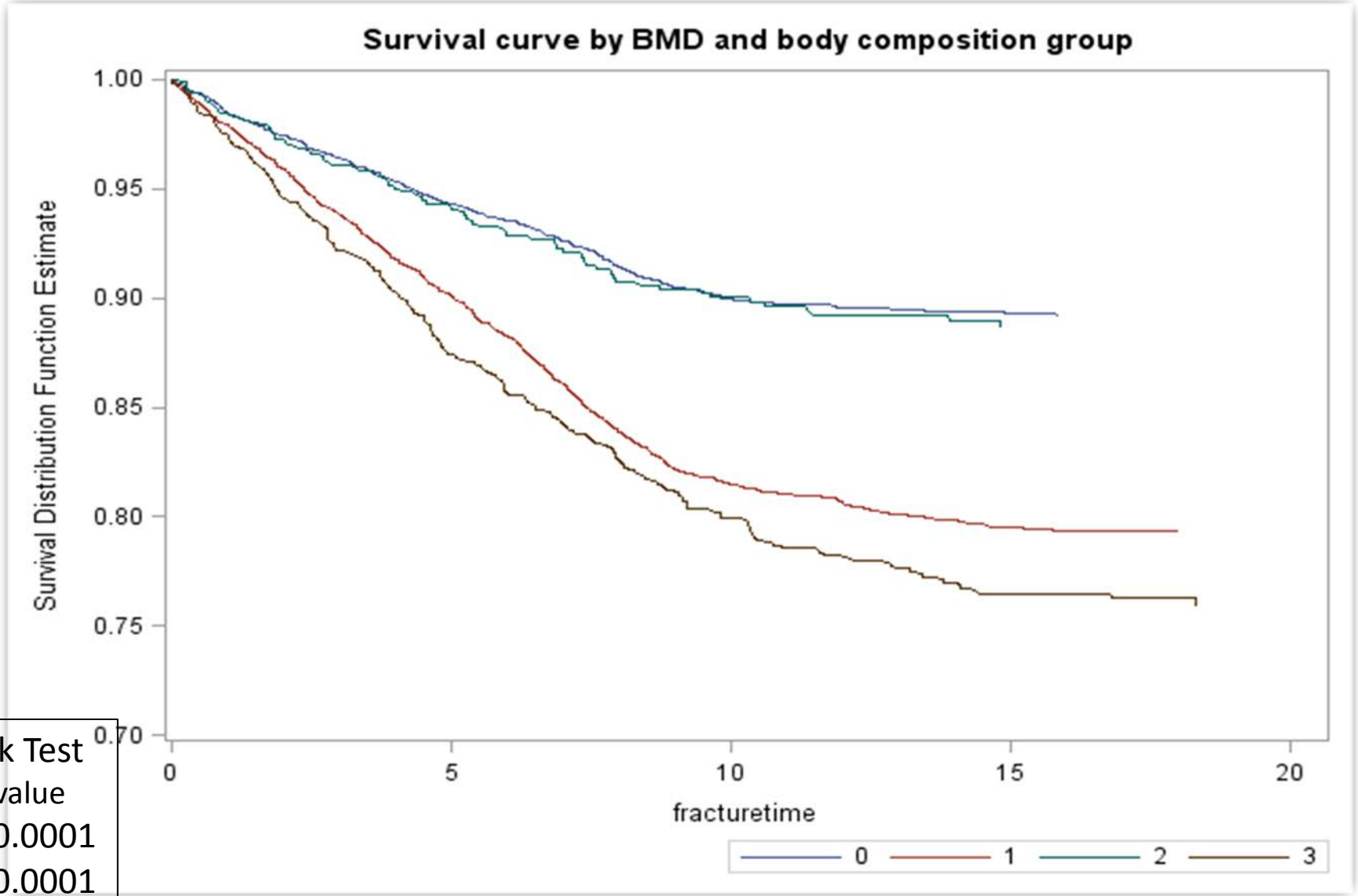
Group	Hip Fractures (n=)	Lower Extremity Fractures [1] (n=)	Total LE (including hip) (n=)	Lower Arm fractures[2] (n=)
Referent	38	147	185	75
Sarcopenia	8	33	41	12
Low BMD	207	264	471	214
Sarcopenia +Low BMD	70	95	165	65

- [1] Fractures of the tibia and fibula, tibial plateau, patella, femur, ankle, self-report LE fracture
- [2] Fractures of the radius & ulna, wrist/carpal, self-report lower arm fracture

Statistical Approach

Cox Proportional Hazards Model

- Base model- adjusted for age, race, and clinic site
- Multi-variable model-base model + physical activity, physical function, corticosteroid use, smoking status, alcoholic consumption, history of falls, history of fracture, hormone use, dietary calcium intake, dietary vitamin D intake, treated diabetes
- Participants with no sarcopenia and normal BMD were the reference group
- Median follow up time was 15.9 years



Log Rank Test	pvalue
0 vs 1	<0.0001
0 vs 2	<0.0001
0 vs 3	<0.0001
1 vs 2	<0.0001
1 vs 3	0.0056
2 vs 3	<0.0001

0= referent
1= low bmd
2= sarcopenia
3= combination

Results: Risk of Fracture by BMD and Body Composition Group

Group	Base Model	Multi-variable Model*
	Hazard Ratio (95% Confidence Interval)	
No Sarcopenia or low BMD	REF	REF
Sarcopenia	0.92 (0.72-1.17)	0.85 (0.64-1.12)
Low BMD	1.57(1.38-1.78)	1.59(1.38-1.84)
Low BMD and Sarcopenia	1.76 (1.50-2.07)	1.72 (1.44-2.06)

Interaction between sarcopenia and bone density not significant

*adjusted for age, race, study assignment, clinic site physical function, history of fracture, history of falls, hormone use, physical activity, alcohol consumption, smoking status, corticosteroid use, treated DM, dietary calcium intake, dietary vitamin D intake

Discussion

Women with low BMD, irrespective of their sarcopenia status, have higher risk of fracture compared to women with normal BMD and normal ALM

The presence of sarcopenia does not increase the risk of fracture in women

Results similar to those found previously by Chaloub et al that the combination of sarcopenia and low bone density did not increase the fracture risk significantly

Discussion

The difference in fracture risk may suggest that there is a sex difference in the role of sarcopenia and fracture risk

- Potentially the decline in lean mass and strength is not as significant in women compared to men
  - ? Loss of testosterone having a significant impact

- The age of the women in this study may not have been old enough to detect a greater decline in lean mass
- Are there other factors that drive the process of sarcopenia- such as neuromuscular innervation, chronic inflammation, changes in fat metabolism

Discussion

Are there other factors that drive the process of sarcopenia?

- neuromuscular junction degeneration & mitochondrial dysfunction
- chronic inflammation
- changes in fat metabolism

Summary

In conclusion, we did not find an increase in fracture risk in women with both sarcopenia and low bone density

Low bone density remains a strong risk factor for fracture

Strengths

+ Well-established multi-ethnic cohort with validated measures of body composition
+ Extended period of follow-up
+ Adjudicated fractures
+ Control for other potential confounders

Limitations

- Controversy with definition of sarcopenia
- Unable to use physical function measures due to small sample
- WHI cohort has “healthy” younger women (sarcopenia only accounted for ~7% of the sample)
- Not enough power to detect differences across race

Thank you

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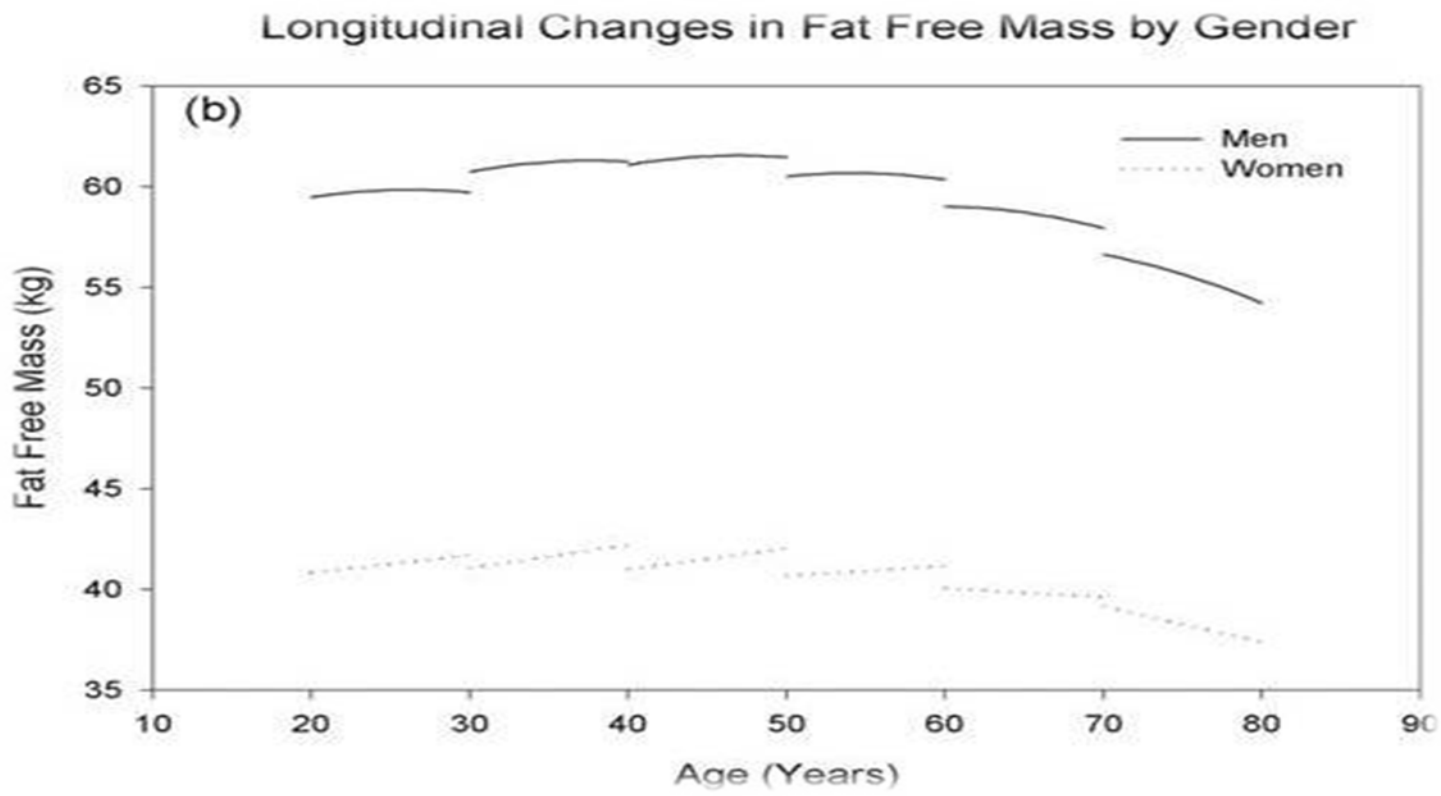
References

http://www.cdc.gov/nchs/data/nhanes/databriefs/osteoporosis.pdf


Longitudinal Changes in Fat Free Mass by Gender
(b)
Men
Women
Fat Free Mass (kg)
65
60
55
50
45
40
35
10
20
30
40
50
60
70
80
90
Age (Years)